

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

PL 03520

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#376
A review of PP# 7F1918 and 7H5160
proposing the establishment of
Tolerances in/on citrus.

Robert Coberly, Biologist
Toxicology Branch

Robert Coberly 5/16/77

Mr. Franklin Gee
PM #16

Pesticide Petition No.: 7F1918

Food Additive Petition No.: 7H5160

EPA Reg. No.: 201-274

Petitioner: Shell Chemical Company.

Chemical Name: Dimethylphosphate of 3-hydroxy-N,N-dimethyl cis
crotonamide.

Synonyms: A) Parent Chemical

Bidrin, dicrotophos, SD3562, CAS 141-66-2, ENT-24482,
3-(dimethoxyphosphinyloxy)-N,N-dimethyl-cis-crotonamide.

B) Metabolite

Azodrin, 3-(dimethoxyphosphinyloxy)-N-methyl-cis-
crotonamide, monocrotophos, SD 9129, CAS 919-44-8,
and ENT-27129; 3-hydroxy-N-methylcrotonamide dimethyl
phosphate; dimethyl phosphate, ester with cis 3-hydroxy
-N-methylcrotonamide; dimethyl 1-methyl-2-(methyl-
carbamoyl)-vinyl phosphate, cis.

Action Requested: The petitioner proposes that the following tolerances
be established for the residues of dimethyl phos-
phate of 3-hydroxy-N,N-dimethyl cis crotonamide
(azodrin) and its metabolites, dimethyl phosphate of 3-
hydroxy-N-methyl-cis crotonamide and crotonamide,
3-hydroxy-N-methyl-cis dimethyl phosphate in or
on citrus fruit.

0.5 ppm in or on citrus fruits (PP# 7F1918)
1.0 ppm in citrus dry pulps (FAP# 7H5160)

Recommendations: Toxicology cannot recommend the establishment of
the requested tolerances. See also other conditions

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Related Petitions and Established Tolerances:

- A) Petition numbers for dimethyl phosphate of 3-hydroxy-N,N-dimethyl cis crotonamide are 7G0571, 1F0162 and 6F1675.
- B) Established tolerances for (Bidrin) dimethyl phosphate of 3-hydroxy-N,N-dimethyl cis crotonamide are listed in 40 CFR 180.299 and are as follows:
- 0.05 ppm in or on cottonseed.
- C) Petition numbers for the metabolite (Azodrin) dimethyl phosphate of 3-hydroxy-N-methyl-cis-crotonamide are 6F0491, 6G0497, 0F0912, 3F1348 and 4F1515.
- D) Established tolerances for the metabolite dimethyl phosphate of 3-hydroxy-N-methyl-cis-crotonamide are listed in 40 CFR 180.296 and are as follows:
- 0.05ppm in or on peanuts.
 0.1 ppm in or on cottonseed.
 0.1 ppm in or on potatoes.
 0.5 ppm in or on tomatoes.
 0.5 ppm in or on peanut hulls.
 0.1 ppm in or on sugarcane.

Components of typical technical BIDRIN^R Insecticide production are given below:

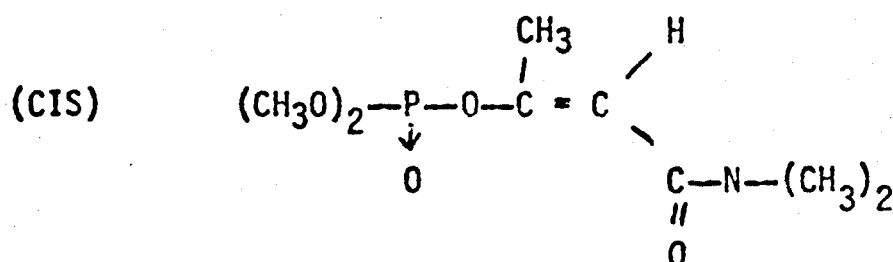
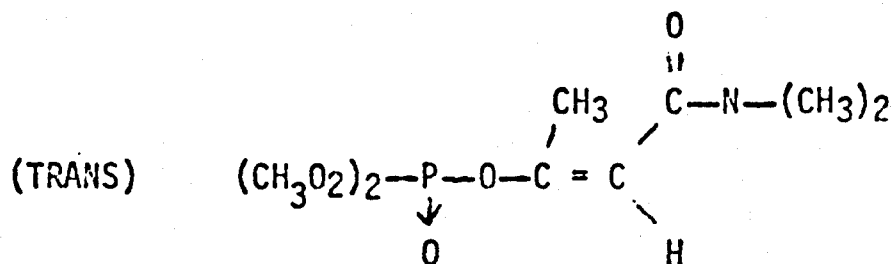
<u>No.</u>	<u>Component</u>	<u>Percent by Weight</u>
1)	3-(dimethoxyphosphinyloxy)-N,N-dimethyl-cis-crotonamide (cis or alpha isomer)	87
2)	3-(dimethoxyphosphinyloxy)-N,N-dimethyl-cis-crotonamide (trans or beta isomer)	6
3)	N,N-dimethylacetoacetamide	1
4)	N,N-dimethyl-2-chloroacetoacetamide	3
5)	N,N-dimethyl-2,2-dichloroacetoacetamide	1
6)	3-(dimethoxyphosphinyloxy)-2-chloro-N,N-dimethyl-crotonamide	1
7)	Unidentified Impurities	1
TOTAL		100

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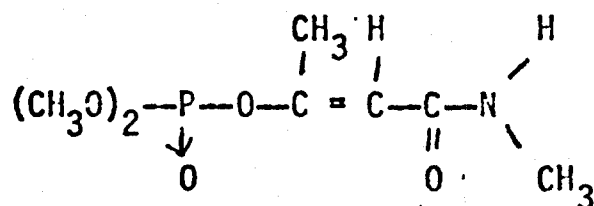
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Chemical Structures:

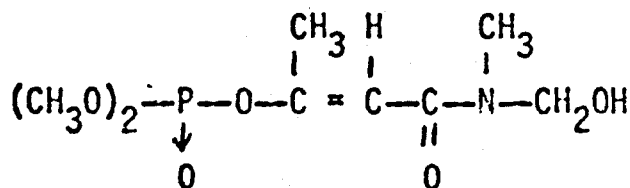
BIDRIN



AZODRIN - a metabolite of Bidrin



Crotonamide, 3-hydroxy-N-(hydroxymethyl)-
-N-methyl-, cis, dimethyl phosphate
 a metabolite of Bidrin

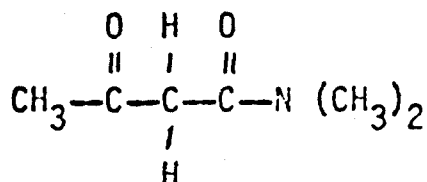


(a tertiary amine)

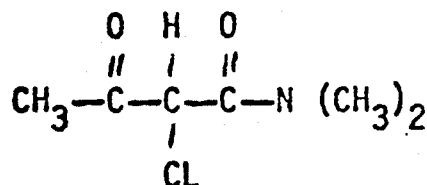
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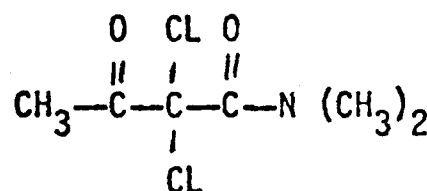
N,N-dimethylacetoacetamide - a compound of Typical Technical Bidrin
(a tertiary amine)



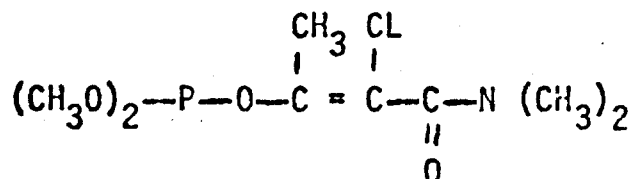
N,N-dimethyl-2-chloroacetoacetamide - a component of Typical Technical Bidrin (a tertiary amine)



N,N-dimethyl-2,2-dichloroacetoacetamide - a component of Typical Technical Bidrin (a tertiary amine)



3-(dimethoxyphosphinyloxy)-2-chloro-N,N-dimethyl-crotonamide -
a component of Typical Technical Bidrin (a tertiary amine)



Formulation: Bidrin 8 Water Miscible Insecticide

Inert ingredient information may be entitled to confidential treatment

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Active Ingredient

94% 3-(dimethoxyphosphinyloxy)-N,N-dimethyl-cis-crotonamide.

Inert Ingredient

[REDACTED]

* Cleared under 40 CFR 180.1001 (C)

Use: Insecticide for seed crop soybean and field crop cotton.

Application Rate: 4.0 to 16 fluid ounces per acre.

Application Method: Spray by airplane or ground equipment.

Application Frequency: Repeat as necessary for soybean and cotton.
Do not apply more than 2 applications per growing season for citrus.

Application Restrictions: Soybeans - do not apply within 30 days of harvest. Do not graze livestock on treated fields, or feed treated trash or seed. Do not apply during peak bee activity. Do not use Bidrin on this crop unless grown for seed.

Cotton - do not apply within 30 days of harvest. Do not graze livestock on treated fields or feed treated gin trash.

Citrus - Do not graze livestock in treated groves. Do not sprinkle irrigate within 72 hours after treatment if irrigation water contacts foliage. Do not apply to groves with standing water, to head ditches containing water or to irrigation ponds. Do not apply to weedy groves or to weedy field borders. Do not apply after July 1. Do not apply when birds or wildlife are observed feeding in the grove.

General - Keep out of lakes, ponds and streams. Avoid spray drift. Do not spray when windy.

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Toxicity Data

The following toxicological data were submitted by Shell Chemical Company in support of prior request for tolerances:

- ✓ Acute Rat Oral : LD₅₀ = 22 mg/kg (range 19-25)
Symptoms were typical of organophosphate poisoning.
- ✓ Acute Rat Oral (Tech) : LD₅₀ = 12.8 mg/kg (9.1-15.7)
- ✓ Acute Rat Oral : LD₅₀ = 28.7 mg/kg
(Isopropyl Alcohol as solvent)
- ✓ Acute Rat Oral : LD₅₀ = 30.2 mg/kg
(Dimethyl sulphoxide as solvent)
- ✓ Acute Mice Oral : LD₅₀ = 15 mg/kg - typical
symptoms of organophosphate poisoning were noted.
- ✓ Acute Mice Oral : LD₅₀ = 20 mg/kg
(Isopropyl Alcohol as solvent)
- ✓ Acute Mice Oral : LD₅₀ = 40-50 mg/kg
(Dimethyl sulphoxide as solvent)
- Acute Duck Oral : LD₅₀ = 2.5-5.0 mg/kg
- Acute Fowl Oral : LD₅₀ = 10-12.5 mg/kg
- ✓ Acute Rat Inhalation (Tech) : LC₅₀ = 0.65 mg/L
- ✓ Acute Rat Inhalation : LC₂₀ ≈ 0.86 mg of AI/L. No
(38% Solution) deaths were reported at
0.81 mg of AI/L
- ✓ Acute Rat Dermal (Tech) : LD₅₀ = 0¹ 136 mg/kg
: 0¹ 111 mg/kg
- ✓ Acute Guinea Pig Antidote (Tech) : LD₅₀ = 45 mg/kg
- ✓ Acute Rabbit Dermal : LD₅₀ = 224 mg/kg - tremors,
salivation noted within
24-48 hours.

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- Acute Hen Dermal : LD₅₀ = 7.4 mg/kg
- ✓ Acute Rabbit Eye Irritation : Erythema noted within 30 seconds of application - normal in 24 hours.
- ✓ Antidote Study (Rat) : Atropine plus toxogonin produced best effect
- ✓ Antidote Study (Guinea Pig) : Atropine alone or in combination with P-2S (2-hydroxyiminomethyl-N-methylpyridinium methane sulphonate) is an effective antidote
- ✓ 2 Week Rat Feeding : Cholinesterase activity was depressed at all dosage levels tested (10-4000 ppm)
- ✓ 6 Week Rat Cholinesterase : Plasma cholinesterase inhibition was noted at all dosage levels (5-40 ppm)
- ✓ 12 Week Rat Cholinesterase : NEL = 0.5 ppm ✓
- ✓ 12 Week Rat Feeding : Systemic NEL = 45 ppm
- 3.5 Week Dog Feeding : Whole blood ChE NEL = 1.5 ppm
RBC cholinesterase NEL = >4.5 ppm
Plasma ChE NEL = 1.5 ppm
- ✓ 13 Week Dog Feeding : Systemic NEL ≥ 50 ppm
Brain and RBC cholinesterase NEL = 5 ppm
Plasma cholinesterase NEL = <1 ppm
- ✓ 21 Day Rabbit Dermal : Negative local skin reaction at 40 mg/kg/day (highest level tested). Twenty percent mortality reported at 40 mg/kg/day level.

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- ✓ Rat Potentiation Study : Some potentiation was noted when Bidrin was used in combination with other O.P.'s such as malathion, dimethoate, guthion, Co-Ral, methyl parathion and ronnel.
- ✓ 21 Day Demyelination In Chickens : Did not induce demyelination of the peripheral nerves at the level of 0.74 mg/kg/day (1/10 the LD50)
- ✓ One Generation Rat Reproduction : NEL = 3.0 ppm. A level of 35 ppm caused some reduction in female fertility and viability of the offspring
- ✓ Three Generation Rat Reproduction : Reproductive NEL = 2 ppm. CNS conditions noted in some pups at 50 ppm.
- ✓ Rat Teratogenic Study : NEL \geq 100 ppm. It is suggested that Bidrin may interfere with implantation and placentation at 50 ppm and 100 ppm.
- ✓ 2 Year Rat Feeding : Systemic NEL = 10 ppm. PBC and brain cholinesterase inhibition NEL = 1.0 ppm
- ✓ 2 Year Dog Feeding : Systemic NEL = 16 ppm. RBC cholinesterase inhibition NEL is 1.6 ppm
- ✓ Human Toxicity : Under practical field exposure RBC and blood plasma levels in 29 persons were normal. The calculated exposure was 0.0016 mg/kg body weight
- ✓ Metabolism Studies : Orally treated rats excreted 63-71% of the radioactivity within 48 hours with azodrin as the major metabolite. Dog and goats treated orally and mice and rabbits treated

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Intraparietally exhibited the same metabolic pattern although the rates of excretion differed. Milk from Bidrin fed goats contained Azodrin as a metabolite in larger amounts than the parent compound

Fate of Bidrin in Cows : Milk and feces from cows fed bidrin at 0.25 mg/kg (about 6 ppm) for 28 days were negative. Azodrin was present in urine of all four tested cows at 17-21 days on treatment.

In-vitro Study : Bidrin was shown to inhibit brain ChE more than RBC by a factor of 1.3

Conclusions

In the May 21, 1971 review by Dr. Clara H. Williams, the 2 year rat feeding no-effect level of 1.0 ppm was chosen and used to support the calculated ADI of 0.005 mg/kg/day ($1.0 \text{ ppm} \div 10 \text{ [ChE safety factor]} = 0.1 \text{ ppm} \times 0.05 \text{ [rat conversion factor]} = 0.005 \text{ mg/kg/day}$). The two year dog feeding no-effect level of 1.6 ppm was not used because the no-effect level was higher than the rat's no-effect level and the study is considered short of being classified as a life time study.

However, when the calculation factors used to determine the ADI are applied to the dog data, the following values are brought to light: $1.6 \text{ ppm (dog NEL)} \div 10 \text{ (ChE safety factor)} = 0.16 \text{ ppm} \times 0.025 \text{ (dog conversion factor)} = 0.004 \text{ mg/kg/day}$. The $0.004 \text{ mg/kg/day (ADI)} \times 60 \text{ kg (human body weight)} = 0.24 \text{ mg/day}$ as the permissible intake for a 60 kg human in a daily diet of 1.5 kg of food.

When the same calculations are conducted on the rat values, we find the following: $0.005 \text{ mg/kg/day (ADI)} \times 60 \text{ kg (human body weight)} = 0.30 \text{ mg/day}$ as the permissible intake for a 60 kg human in a daily diet of 1.5 kg of food.

Admittedly the difference between 0.24 mg/kg and 0.30 mg/kg is negligible. However, this reviewer recommends the 0.24 mg/kg be utilized to limit the residue levels of bidrin in treated PAC's.

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The amount of Bidrin added to the diet from the established tolerance is considered negligible (Dr. C. Williams review of 5/21/71). The amount of Bidrin added to the diet from the proposed tolerance of 0.5 ppm in citrus would be 0.03 mg/day, which is considered the total of the maximum theoretical exposure (ITE).

The following areas must be addressed before consideration of this requested tolerance can proceed.

- 1) What amount of azodrin will be present in or on the citrus as a direct result of treatment with bidrin?
- 2) If azodrine is a residue on the treated citrus, at what residue level will the petitioner request a tolerance?
- 3) What amount of the non-phosphorus containing portion of the molecule (ie: the N,N-dimethyl acetoacetamide moiety) will remain as a residue on the treated crop (see Chemistry Branch review of 1/26/76 from Mr. Donald Reed to PM #15, page 1 #1a)?
- 4) Will the use of bidrin on soybeans grown for seed use only result in residues in the crop grown from the treated seed crop intended for human use?
- 5) The letter of October 6, 1976 from PSO to Pesticide Registration Officer, Dr. Martin Rogoff recommended that registration actions on secondary and tertiary amines be suspended.
- 6) The letter of October 20, 1976 from the Associate Director For Registration Division to the Product Branch Chiefs subjected "Registration Actions on Chemicals Potentially Containing Nitro-samines" states that registration actions should be withheld until further notice is received.
- 7) The human precautionary statements on the proposed label of Bidrin 8 Water Miscible EPA No. 201-274 as reviewed must be together and not separated by fish and wildlife precautionary statements.



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034234

Chemical: Dimethyl phosphate ester with 3-hydroxy-

PC Code: 035201

HED File Code 13000 Tox Reviews

Memo Date: 05/06/77

File ID: TX000095

Accession Number: 412-03-0107

HED Records Reference Center
03/19/2003